Remarks

This Reply is timely filed within three months of the mailing date of the latest non-final Office Action. Reconsideration of this Application is respectfully requested.

Claims 37, 39-44, 46, 48, 49, 56, 58, 72, and 77-88 are pending in the application, with claims 37, 49, and 56 being the independent claims. Claims 50-55, 57, 59-71, and 73-76 stand withdrawn as being directed to non-elected species. Claim 88 is sought to be added. Claim 45 is sought to be canceled without prejudice to or disclaimer of the subject matter therein. Claims 1-36 and 47 have previously been cancelled.

Applicants have amended claim 37 to delete the term "731-740" and to insert instead the term "727-744". In addition, claim 37 has been amended to include "SEQ ID NO: 15" for a region corresponding to sequence 727-744 of the C5 component of human complement. Support for this amendment can be found on page 7, [0073], of the published U.S. application. Claim 44 had been amended to delete the phrase "or their allelic variants." Claim 49 has been amended to delete a limitation "or protein sequences having at least 95% homology to said sequences." Applicants have also amended claim 72 to delete the term "731-740" and to insert instead the term "727-744", and to delete the limitation "an antibody with at least 95% homology with at least one of the amino acid sequences corresponding to SEQ ID NO:2, SEQ ID NO:4, or SEQ ID NO:6." Support for this amendment can be found on page 7, [0073], of the published specification. Claim 72 has been amended to correct a typographical error. Additionally, Applicants added claim 88, support for which can be found on pp. 6-7,

[0071], of the specification. These changes are believed to introduce no new matter, and their entry is respectfully requested.

The substitute sequence listing is submitted on a compact disc in ASCII text file as part of an associated file. Applicants' attorney hereby states that the changes made in the sequence listing do not include new matter in accordance with 37 C.F.R. § 1.825(a).

Based on the above amendments and the following remarks, Applicants respectfully request that the Examiner reconsider all outstanding objections and rejections and that they be withdrawn.

Sequence Compliance

The Examiner objected to the disclosure of the application as not complying with the allegedly enclosed Notice to Comply With Requirements For Patent Application Containing Nucleotide Sequence And/Or Amino Acid Sequence Disclosure. Applicants respectfully contend that no Notice was attached to the Office Communication. However, to address sequence non-compliance issues set forth in the Office Action, Applicants submit herewith a Substitute Specification, wherein all listed sequences are believed to have corresponding SEQ ID NOS. Additionally, Applicants submit herewith a Substitute Sequence Listing which provides for the peptides listed in the specification, as filed, but not appearing in the original Sequence Listing. In light of these submissions, Applicants respectfully request that the above objections be withdrawn.

The Rejection under 35 U.S.C. § 112, second paragraph

Claims 37, 39-46, 48-49, 56, 58, 72, and 77-78 are rejected under 35 U.S.C. § 112, second paragraph, as "being indefinite and failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention." (OA at p. 3.)

Specifically, the Examiner stated that the claims are indefinite because no SEQ ID NO(S) are recited for sequence of 731-740 of the C5 component of human complement. Applicants believe that the present amendments render this rejection moot, and its withdrawal is respectfully requested.

The Rejection under 35 U.S.C. § 112, first paragraph

The Examiner rejected claims 81-83, 85-87, 89-91, and 93-94 under 35 U.S.C. § 112, first paragraph, because the specification allegedly does not contain a written description of the claimed invention. Applicants respectfully traverse this rejection.

Specifically, the Examiner stated that the phrases "a region having at least 80%/95% homology thereto," "allelic variants," and "conservative mutations" are not supported by an adequate written description, because "given the well known high level of polymorphism of immunoglobulins/antibodies, the skilled artisan would not have been in possession of the vast repertoire of antibodies and the unlimited number of antibodies encompassed by the claimed invention." (OA at p. 4.)

Applicants note that claims 89-91 or 93-94 are not pending in the present application. Therefore, Applicants respectfully contend that the rejection of these claims was improper. In addition, claim 81 does not contain any of the terms "homologous

entities," "allelic variants," "conservative mutants," or the like. Therefore, Applicants respectfully contend that the rejection of claim 81 for the reasons detailed in the Office Action is also improper.

The terms "allelic variants," "conservative mutants," or the like are not found in any of the claims 82-83 or 85-87. Rather, these terms appear only in claim 44 of the presently pending claims. Solely to advance prosecution, and not in acquiescence to the Examiner's rejection or intended rejection, Applicants have amended claim 44 without prejudice or disclaimer to delete the term "allelic variants." The term "a region having at least 95% homology thereto" is found in claims 45, 49, 72, and 82-87. Solely to advance prosecution, and not in acquiescence to the Examiner's rejection or intended rejection, Applicants canceled claim 45 and amended claims 49 and 72 without prejudice or disclaimer to delete this term.

The Examiner has noted the well-described dependence of proper antibody (Ab) binding to an epitope on precise amino acid sequences of the Ab and the epitope. As such, the Examiner asserted that a genus of Abs and/or epitopes characterized by the terms "conservative mutants" and "homologous entities" cannot be adequately described without providing "a sufficient description showing possession of the necessary functional characteristics coupled with a known or disclosed correlation between function and structure." (OA at p. 5.) The Examiner further stated that the Applicants did not describe which residues of the claimed epitope and/or Ab are required to be substantially the same in order for the Ab to retain appropriate specificity to the epitope. (OA at p. 6.)

Contrary to the Examiner's assertions, Applicants did present an adequate description to the presently claimed genus of Ab and/or epitopes. Under *Falkner v. Inglis* 448 F.3d 1357 (Fed. Cir. 2006), the Federal Circuit held that neither an actual reduction to practice, nor working examples are required in the specification to comply with the written description requirement. Instead, "the [written description] requirement may be met by disclosure of relevant, identifying characteristics." (The Guidelines for the Examination of Patent Application Under the 35 U.S.C. 112, § 1 "Written Description" Requirement.) Applicants respectfully contend that the specification guides the skilled artisan through "relevant, identifying characteristics" of the genus, said characteristics being an ability of the claimed Ab to retain its specificity towards the claimed epitope, which is achieved by introducing ***conservative mutations*** into the provided Ab sequences (claim 44), or providing ***greater than 80% homologues*** to SEQ ID NO: 15 (claims 37-46, 72, 77-80, and 85-87).

Specifically, Applicants provided a disclosure that "enclosed in this scope of the present invention [are] the amino-acid sequences obtained by mutation of the sequences contained in the annexed Sequence Listing, as long as these mutation ***do not alter the described anti-C5 antibody specificity***." (Page 4, [0049], of the specification, emphasis added.) As such, the presently claimed genus of antibodies does not encompass "***the vast*** repertoire of antibodies and ***the unlimited*** number of antibodies", but is limited only to Abs that retain their specificity to the region 727-744 of the C5 component of human complement. Similarly, the presently claimed genus of epitopes is limited only to those that are specifically recognized by the claimed antibodies. This is achieved by, for example, introduction of conservative mutations into the provided sequences.

Applicants respectfully draw the Examiner's attention to the specification's definition of the term "conservative mutation":

> The mutation can be "conservative", when it is based on an amino-acid with similar structural or chemical characteristics with respect to polarity, charge, solubility, hydrophobicity, hydrophilicity or it is based on the amphipatic nature of the amino-acid residues involved. For instance groups of amino acids sharing similar characteristics of polarity are composed by non-polar (hydrophobic) aa which include alanine, leucine, isoleucine, valine, proline, phenylalanine, tryptophan and metionine; non-polar or neutral amino acids that include: glycine, serine, threonine, cysteine, tyrosine, asparagine and glutamine; positively charged (basic) amino acids that include: arginine, lysina [sic] and histidine; and the group of negatively charged (acidic) amino acids that comprises: aspartic acid and glutamic acid.

Present specification, page 4, [0049].

Therefore, a person skilled in the art would understand that introduction of the conservative mutation(s) into the SEQ ID NOS: 4 and/or 6, as required by claim 44, would not be expected to alter the specificity of the claimed antibodies to the claimed epitope, because the overall structure and chemical characteristics of the resulting polypeptide would be very similar to the original sequence. Furthermore, in *Noelle v. Lederman*, 355 F.3d 1343 (Fed. Cir. 2004), the court held that the structure of an antibody is fully described by the structure (*i.e.,* the sequence) of the antigen. As applied to the present application, the sequence of the epitope is provided. It follows then, under *Noelle v. Lederman*, that sequence of the epitope defines the structure of an antibody that binds to such epitope of C5.

Specific recognition of the claimed epitope by the claimed Ab can also be achieved by providing greater than 80% homologues of SEQ ID NO:15, as recited in claim 37 of the present invention. The claimed sequence of SEQ ID NO: 15 contains

eighteen amino acids. Greater than 80% homology to this sequence is achieved by varying, at most, only three amino acids at a time. This small genus is properly described in the present specification, because it is coupled to the functional limitation that it must be recognized by the claimed antibody, and the antibody must inhibit the conversion of the C5 alpha chain to C5a and C5b.

In addition, the present disclosure tested the ability of the claimed antibody to inhibit conversion of C5 to C5a in various species. (Example 9 and Figure 5.) Specifically, the claimed antibody was shown to be able to inhibit a hemolytic activity present in serum of all animals tested, namely man, rat, rabbit, and mouse. Applicants are providing herewith an alignment of the sequence corresponding to SEQ ID NO: 15 with corresponding sequences from *P. troglodytes*, *M. mulatta*, *B. taurus*, *S. scrofa*, *M. musculus*, and *R. norvegicus* (Exhibit A). As evident from the alignments, the lowest identity exists between sequences derived from *H. sapience* and *R. norvegicus* (61%). However, Example 9 clearly indicates that the claimed antibody is able to recognize an epitope that is only 61% identical to SEQ ID NO:15 (rat) and 80% identical to SEQ ID NO:15 (mouse) . Therefore, not only have Applicants described the defining properties of the epitope (*i.e.*, 80 % homology to SEQ ID NO:15 and it must be recognized by the claimed antibody), but they also provided a sufficient number of species of the larger genus (*i.e.*, epitopes from rat, mouse, and rabbit). As such, the written description requirement for the term "80% homology to SEQ ID NO:15" is met.

Therefore, Applicants assert that they were in fact in possession of the structural characteristics of a representative number of species possessed by the members of the

claimed invention. Accordingly, Applicants respectfully request that the rejection be reconsidered and withdrawn.

The Rejection Under 35 U.S.C. § 102

Claims 37, 39-40, 56, 58, 72, and 80-83 are rejected under 35 U.S.C. § 102 (b) as allegedly being anticipated by Evans, *et al.* (U.S. Patent No. 6,355,245). Specifically, the Examiner stated that Evans teaches human C-5 specific antibodies, "wherein the antibodies should prevent the cleavage of C5 to form C5a and C5b." (OA at p. 7). As such, Evans *et al.* are alleged to teach an antibody that targets the same or nearly the same cleavage cite, and the burden is on Applicants to demonstrate otherwise. Applicants respectfully traverse the rejection.

"A claim is anticipated only if each and every element as set forth in the claim is found, either expressly or inherently described, in a single prior art reference." *Verdegaal Bros. v. Union Oil Co. of California,* 814 F.2d 628 (Fed. Cir. 1987); MPEP 2131. "To establish inherency, the extrinsic evidence 'must make clear that the missing descriptive matter is necessarily present in the thing described in the reference, and that it would be so recognized by persons of ordinary skill. Inherency, however, may not be established by probabilities or possibilities. The mere fact that a certain thing may result from a given set of circumstances is not sufficient.'" *In re Robertson*, 169 F.3d 743, 745 (Fed. Cir. 1999). Also, "[a]n invitation to investigate is not an inherent disclosure" where a prior art reference "discloses no more than a broad genus of potential applications of its discoveries." *Metabolite Labs., Inc. v. Lab. Corp. of Am. Holdings*, 370 F.3d 1354, 1367, 71 USPQ2d 1081, 1091 (Fed. Cir. 2004) (explaining that "[a] prior art reference that discloses a genus still does not inherently disclose all species within that broad category"

but must be examined to see if a disclosure of the claimed species has been made or whether the prior art reference merely invites further experimentation to find the species).

Evans *et al.* contains a general teaching that one can raise an antibody against C5 and a specific teaching of one such antibody (5G1.1). Neither teaching anticipates the claimed invention. In regards to the general teaching that one can raise Abs against C5, Applicants claim here a specific antibody that recognizes and binds a region corresponding to sequence 727-744 (SEQ ID NO:15) of the C5 component of human complement, which results in an inhibition of the conversion of the C5 alpha chain to C5a and C5b. That antibody is not disclosed in and therefore not anticipated by the general teaching of Evans *et al.* In regards to the specific 5G1.1 antibody, the Examiner seems to have taken the position that that Ab may inherently anticipate the claimed invention. However, as shown in Example 13 of Evans *et al.*, the 5G1.1 antibody does not bind to the peptides corresponding to the C5a cleavage site.

Although Evans *et al.* teach human antibodies that prevent cleavage of C5 to form C5a and C5b, the disclosure does not contain each and every element as set forth in the presently rejected claims. Specifically, Evans *et al.* do not expressly teach an antibody that "recognizes a region corresponding to sequence 727-744 (SEQ ID NO:15) of the C5 component of human complement or a region having at least 80% homology thereto." The Examiner also acknowledged that *Evans et al.* "does not explicitly teach the amino acid residues 731-740 of C5." (OA at p. 8.) The Examiner stated that "it is Applicant's burden to show that the reference antibody [5G1.1] does not bind or cross-react with the same cleavage site or epitope." (OA at p. 8.). However, Evans *et al.*

themselves provide the requested showing in Example 13 of the patent. Their attempts to characterize an epitope recognized by the referenced antibody yielded negative results, with the only conclusion being that "peptides corresponding to the C5a cleavage site did not bind to the 5G1.1 antibody." (Col. 53, ll. 14-15). Therefore, the disclosure of Evans *et al.* does not expressly anticipate the claimed invention.

Nor does it provide an inherent disclosure of the claimed antibody. Under *Robertson v. Scripps*, the disclosure of Evans *et al.* does not inherently anticipate the claimed invention, because it does not establish that the missing requirement of Ab binding to the specific SEQ ID is ***necessarily*** a characteristic of the reference Ab (as evidenced in Example 13).

In addition, Evans *et al.* do not enable the claimed antibody. Anticipation requires a prior art reference to be enabling such that the claimed subject matter may be made or used by one skilled in the art. *Amgen Inc. v. Hoechst Marion Roussel, Inc.*, 314 F.3d 1313, 1354 (Fed. Cir. 2003). A reference is enabling if it teaches those of ordinary skill in the art enough that they can carry out the invention without "undue experimentation." *Elan Pharmaceuticals, Inc. v. Mayo Foundation,* 346 F. 3d 1051, 1057 (Fed. Cir. 2003).

Evans *et al.* do not enable a person of ordinary skill in the art to make the claimed isolated polypeptide for at least the following reasons. The anti-C5 antibody disclosed in Evans *et al.* was produced by animal immunization. (Col. 31, l. 55-col 32, l. 3.) Notable difficulty in raising antibodies against conserved proteins regions when taking a classical approach of an immunization of an animal with a peptide corresponding to the conserved region has been much appreciated. Mazari *et al.*, "The cleavage site of C5 from man and

animals as a common target for neutralizing human monoclonal antibodies: *in vitro* and *in vivo* studies," *Eur. J. Immunol.* (2002), 32: 2773-2782 (Attached as Exhibit B), explain:

> Antibodies . . . obtained by immunization are constrained by the limits of the immune system of the animal used for immunization. In particular, it tends to be very difficult to derive antibodies against conserved antigens by immunization.

Mazari et al., p. 2778, col. 1.

Collet *et al.*, "Evolution of mammalian apolipoprotein A-I and conservation of antigenicity: correlation with primary and secondary structure," J. Lipid Res. (1997), 38: 634-644 (Attached as Exhibit C), concur:

> The natural selection that favors the conservation of functionally important proteins is a widely accepted idea in evolutionary theory. The antigenicity index of an important and invariant functional domain in protein is very low whereas the region outside the functional domain vary and can be highly antigenic.

Collet et al., p. 639, col. 2.

Jemmerson *et al.*, "Analysis of an evolutionary conserved antigenic site on mammalian cytochrome c using synthetic peptides," *Proc. Natl. Acad. Sci.* (1985), 82: 1508-15212, (Exhibit D) also note:

> A commonly accepted view of the antigenicity of a protein is that the predominant epitopes correspond to those regions where the immunizing protein differs in amino acid sequence from the homologous protein of the immunized animal. . . . It should be noted, however, that reactivity to this region of cyt *c* may arise from circumstances that are consistent with the hypothesis that conserved regions of proteins are not, in general, immunogenic.

Jemmerson *et al.*, p. 1508, col. 1 and p. 1512, col. 1.

As evidenced by sequence alignments presented in Exhibit A, the epitope located at the cleavage site of C5 is highly conserved between different species (especially mouse and man). Therefore, introduction of the peptide corresponding to SEQ ID NO: 15 of Evans *et al.* into an animal (*i.e.*, a mouse), is unlikely to result in a production of antibodies against this peptide. Stated otherwise, the disclosure of Evans *et al.* does not teach a person of ordinary skill in the art to obtain an antibody to an epitope with low immunogenicity without an undue experimentation, and is, thus, not enabling.

For the reasons stated above, Applicants acknowledge that Evans *et al.* does not expressly or inherently anticipate the claimed invention. Accordingly, Applicants respectfully request that the rejection be reconsidered and withdrawn.

The Rejections Under 35 U.S.C. § 103

The Examiner rejected claims 37, 39-40, 56, 58, 72, and 80-83 under 35 U.S.C. § 103 (a) as allegedly being obvious over Evans *et al.* (U.S. Patent No. 6,355,245). The Examiner also rejected claims 37, 39-40, 56, 58, 72, and 80-83 under 35 U.S.C. § 103 (a) as allegedly being obvious over Evans *et al.* (U.S. Patent No. 6,355,245), in view of Longberg *et al.* (U.S. Patent No. 5,770,429). The Examiner alleged that one of ordinary skill in the art would have been motivated to make antibodies specific to the C5 cleavage site. Longberg *et al.* disclosure of transgenic mice that produce fully human antibodies to that antigen is alleged to provide further motivation and obviousness for producing human antibodies. Applicants respectfully traverse these rejections.

The factors to be considered under 35 U.S.C. § 103(a), are the scope and content of the prior art; the differences between the prior art and the claims at issue; and the level

of ordinary skill in the pertinent art. *See Graham v. John Deere*, 86 S.Ct. 684 (1966) and MPEP §2141. This analysis has been the standard for 40 years, and remains the law today. *See KSR International Co v. Teleflex Inc.*, 127 S.Ct. 1727 (2007). Under *KSR v. Teleflex*, in order to establish a *prima facie* case of obviousness, it must be shown that all the claimed elements were known in the prior art and one skilled in the art could have combined the elements as claimed by known methods with no change in their respective functions, and the combination yielded nothing more than predictable results to one of ordinary skill in the art.

The Examiner has not met the burden of establishing a *prima facie* case of obviousness. Evans *et al.* alone, or in combination with Longberg *et al.*, do not teach or suggest all of the limitations of the claims. In particular, the cited references do not teach or suggest the antibody that recognizes a region corresponding to sequence 727-744 (SEQ ID NO:15) of the C5 component of human complement, or a region having at least 80% homology thereto, wherein said antibody inhibits the conversion of the C5 alpha chain to C5a and C5b, as discussed in detail under the 102 rejection above.

The Examiner's rejection under 35 U.S.C. § 103(a) is based on the belief that the claimed antibody is inherently present in Evans *et al.*, and that Applicants merely followed "the clear teachings of the prior art to target this specific region." (OA at p. 8.) Applicants respectfully assert that the Examiner's analysis is flawed, because the claimed antibody was not known earlier than the filing date of the claimed invention by Applicants. "Obviousness cannot be predicated on what is not known." *In re Spormann*, 363 F.2d 444, (C.C.P.A. 1966). Evans *et al.* do not disclose an antibody that recognizes specific region spanning amino acids 727-744 (SEQ ID NO:15). In fact, Evans *et al.*

produce and describe an antibody that ***does not*** bind to the specified convertase cleavage cite. Therefore, Evans *et al.* alone is not sufficient to support a *prima facie* case of obviousness of the claimed invention, because it does not teach each and every element of the present claims.

Longberg *et al.* do not cure the deficiencies of Evans *et al.* Longberg merely teaches a method of production of humanized antibodies which is based on immunization of transgenic mice. Longberg *et al.* do not teach or suggest production of an antibody that recognizes a region corresponding to sequence 727-744 (SEQ ID NO:15) of the C5 component of human complement or a region having at least 80% homology thereto, wherein said antibody inhibits the conversion of the C5 alpha chain to C5a and C5b. Therefore, combining Longberg *et al.* with Evans *et al.* does nothing to cure the defects of Evans *et al.* and therefore reliance on this reference can not be used to establish a *prima facie* case of obviousness.

Even assuming *arguendo* that the Examiner had established a *prima facie* case of obviousness (which Applicants do not concede), the unexpected superiority of Applicants' invention over the antibody of Evans *et al.* is sufficient to rebut the *prima facie* case of obviousness based on the disclosure of Evans *et al.*, alone or in combination with Longberg *et al.*

A determination of obviousness under 35 U.S.C. § 103 requires an evaluation of any evidence of secondary considerations such as unexpected results. *Graham v. John Deere,* 383 U.S. 1 (1966); MPEP 2141, p. 2100-113. Even when a claimed compound appears obvious on structural grounds, courts have long recognized "that unexpected properties can show that a claimed compound . . . was not obvious when looked at as a

whole." *In re Mayne*, 104 F.3d 1339, 1342 (Fed. Cir. 1997). "Evidence that a compound is unexpectedly superior in <u>one</u> of a spectrum of common properties . . . can be enough to rebut a *prima facie* case of obviousness." *In re Chupp*, 816 F.2d 643, 646 (Fed. Cir. 1987) (*emphasis added*).

Applicants respectfully point out that the claimed anti-C5 antibody shows unexpectedly superior properties to anti-C5 antibody disclosed in Evans *et al.* In support of this contention, Applicants enclose as Exhibit B an article by Marzari *et al.* As stated in the article, the antibody taught in Evans *et al.* (which, as evident from Example 13 of Evans *et al.*, does not bind to the claimed epitope) "does not seem to be effective on C5 derived from other animals and this precludes its use in animal models, which would be helpful in the evaluation of their in vivo effects prior to use in man." (P. 2777, col. 1). Thus, this cross-reactivity of the claimed antibody is an unexpected and superior property over the Abs disclosed in Evans *et al.*

In addition, Applicants contend that binding of the claimed antibody to a convertase cleavage site of C5 is in itself an unexpected result. An X-ray structure of human complement component C5 has recently been solved by Fredslund *et al.*, "Structure of an influence of a tick complement inhibitor on human complement component 5," *Nature Immun.* (2008), 9:753-760 (attached as Exhibit E). Analysis of the published coordinates reveals that the region corresponding to the convertase cleavage site (*i.e.*, amino acids 727-744, SEQ ID NO: 15) is buried inside the protein and is not readily accessible for binding. For the Examiner's convenience, an image displaying the C5 structure is attached as Exhibit F. For clarity, covertase cleavage site is depicted on the center of the protein whereas only backbone is shown for the rest of

the protein. Therefore, it is highly unexpected that the claimed antibody is able to bind to the region that corresponds to the convertase cleavage site of the intact protein.

Since there was no teaching or suggestion of all the claim limitations in Evans *et al.*, alone or in combination with Longberg *et al.*, a *prima facie* case of obviousness is not established. Furthermore, the claimed invention clearly possesses unexpected superior properties over previously known anti-C5. Accordingly, Applicants respectfully request reconsideration and withdrawal of the rejection.

Conclusion

All of the stated grounds of objection and rejection have been properly traversed, accommodated, or rendered moot. Applicants therefore respectfully request that the Examiner reconsider all presently outstanding objections and rejections and that they be withdrawn. Applicants believe that a full and complete reply has been made to the outstanding Office Action and, as such, the present application is in condition for allowance. If the Examiner believes, for any reason, that personal communication will expedite prosecution of this application, the Examiner is invited to telephone the undersigned at the number provided.

Prompt and favorable consideration of this Amendment and Reply is respectfully requested.

Respectfully submitted,

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